eases. The use of cyclophosphamide, total lymphoid irradiation, and the use of synthetic copolymers are all promising experimental approaches to the treatment of multiple sclerosis. Therapy with monoclonal antibodies directed against specific T-cell subsets and T-cell receptors holds promise.

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Spacers and Reservoirs in Delivery Systems

SPACERS AND RESERVOIRS were developed to aid the delivery of drugs from metered-dose inhalers. These devices, which are attached to the inhalers, should hold the aerosolized spray, making synchronizing between a metered-dose inhaler actuation and inhalation less critical; allow aerosolized droplets to evaporate to a fine mist, delivering the maximal amount of drug to the lungs; and decrease oropharyngeal deposition. β-Adrenergic agonists delivered by metered-dose inhalers in doses of as much as six times those normally recommended, with or without a spacer, give bronchodilation equivalent to nebulizers in patients with acute and chronic asthma, except in some patients with severe asthma.

Delivery to the lung of a whiff by a metered-dose inhaler—at most 15% of each dose—can be improved by holding the inhaler 3 to 4 cm from a wide-open mouth (some authorities prefer the lips to be closed around the mouthpiece), triggering the inhaler during a slow, deep inhalation over five seconds followed by a ten-second breath-hold. Spacers help improve delivery of a drug in a third to half of those patients who cannot correctly use a metered-dose inhaler but add little further therapeutic effect in patients using a proper inhaler technique.

With β-adrenergic agonists, larger spacers with a volume of 750 ml improve bronchodilator response more than smaller spacers. Five spacers are currently available in the United States: Brethancer (Geigy) and Azmacort (Rorer Pharmaceuticals) tube spacers (80 ml and about 100 ml volume) are specifically for terbutaline and triamcinolone metered-dose inhalers; universal add-on devices available are the AeroChamber (Forest Pharmaceuticals), a rigid tube (145 ml); InspirEase (Key Pharmaceuticals), a collapsible bag; and Inhal-Aid (Key Pharmaceuticals), a rigid reservoir (both 700 ml). Other spacers with a pear or cone shape, with about a 750-ml volume and for which there are favorable studies, are not available at present.

Studies with β-adrenergic agonists using Brethancer, AeroChamber, and InspirEase show considerable variation in the effectiveness of these devices relative to a metered-dose inhaler alone. Children using isoproterenol in a metered-dose inhaler with Inhal-Aid achieve bronchodilation equal to that with the use of isoproterenol by intermittent positive pressure breathing. The Azmacort tube spacer, InspirEase, AeroChamber, and Brethancer decrease oropharyngeal deposition, and the latter two have been shown to decrease oropharyngeal thrush from inhaled steroids. AeroChamber has been shown to decrease the dysphonia from inhaled beclomethasone dipropionate.

Physicians should have patients demonstrate their inhaler technique. If it is inadequate or if oropharyngeal thrush or dysphonia from inhaled steroids is a problem, then a spacer, used properly, may be of benefit.

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Methacholine Inhalation Challenge for Diagnosis of Asthma

ASTHMA IS RECOGNIZED CLINICALLY by reversible airway obstruction and airways hyperreactivity. Since the 1940s, bronchial inhalation challenges with pharmacologic and antigenic substances have been used to detect airway hyperreactivity. Bronchoconstriction in patients with asthma can be induced by methacholine, acetylcholine, histamine, carbachol, pilocarpine, serotonin, propranolol, methoxamine, adenosine, prostaglandin D_2 or $F_{2\alpha}$, and leukotrienes C_4 and D_4. Of these, methacholine chloride (Provocholine [Hoffmann La Roche]) has recently been approved by the Food and Drug Administration for inhalation to identify the presence of bronchial hyperreactivity. Methylcholine, a β-methyl homologue of acetylcholine, stimulates the muscarinic receptors on bronchial smooth muscle, increasing bronchomotor activity. Although airways hyperreactivity is present in asthma, the diagnosis is generally made from a combination of history, physical examination findings, and the results of spirometry. Methacholine inhalation challenge is indicated only when the usual evaluation is not diagnostic, such as with patients who have vague symptoms or symptoms such as cough, episodic chest tightness, or atypical dyspnea with normal physical findings and spirometric values. Bronchial challenge may also be used to identify workers who are at risk of occupational asthma developing because of preexisting bronchial hyperresponsiveness. As a research tool, bronchial challenges help clarify the mechanisms of asthma and evaluate new drugs.

Standard procedures for inhaling methacholine have been developed. Factors that influence the response to challenge, such as viral or bacterial respiratory tract infections and pollutants, should be avoided. Various drugs influence the outcome of a challenge, including bronchodilators, cromolyn sodium, and antihistamines. To be challenged, a person should have a baseline forced expiratory volume in one second (FEV_1) of at least 70% of the predicted value. Challenge is done by diluting methacholine from a dry powder and having the patient inhale aerosolized methacholine in ascending concentrations ranging from 0.025 mg per ml of methacholine to 25 mg per ml. Two methods of inhalation are used: five breaths are inhaled from a DeVilbiss nebulizer 646 with a Rosenthal-French dosimeter (0.65 delivery time); or 3 ml of methacholine solution are placed in a

Wright nebulizer and the aerosol is administered continuously for two minutes. After each serial concentration, FEV_1 values are determined, and the procedure ends when there is a 20% or greater fall in the FEV_1 value compared with baseline. Results are expressed as either the provocative dose of methacholine producing a 20% decrease in FEV_1 (PD_{20}), the cumulative dose in breath units (1 breath unit = 1 inhalation of 1 mg per ml of methacholine) producing a 20% decrease in FEV_1, or the area under a dose-response curve. More than 90% of those with asthma respond to methacholine by 200 breath units. Bronchoconstriction following the inhalation of methacholine may also develop in persons with allergic rhinitis, chronic bronchitis, bronchiectasis, and cystic fibrosis, indicating airways hyperreactivity; the provocative or cumulative dose is often larger, however.

Methacholine challenge can be associated with severe bronchoconstriction and should be administered only if oxygen, resuscitation equipment, and inhaled and parenteral bronchodilators are available. It is not a test for routine office use but a useful tool for the evaluation of a person with unexplained respiratory tract symptoms.

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Management of Chronic Idiopathic Urticaria

URTICARIA (HIVES) IS A PRURITIC MIGRATORY ERUPTION characterized by edematous, erythematous wheals of various sizes in the superficial dermis. The term "chronic" refers to symptoms of six weeks' duration or more. Angioedema is a similar reaction confined to the deeper dermis and subcutaneous tissue. The causes of urticaria and angioedema include food, drugs, infection, inhalants, bites and stings, contactants, physical agents, neoplasms, connective tissue disease, and psychic factors. Fatalities from laryngeal edema have been limited almost exclusively to patients with hereditary angioedema and edema due to Hymenoptera stings. Allergy immunotherapy can also result in death. The cause of chronic urticaria usually is not known, hence the term chronic idiopathic urticaria.

For this discussion it is assumed that possible causes have been considered and avoidance has been attempted. Such avoidance may include a diet free of salicylates, benzoic acid derivatives, and tartrazine yellow No. 5, although their potential role in the etiology is controversial. Additionally, potentiating factors such as alcoholic drinks, aspirin, exertion, and heat generally should be avoided. Most patients respond to symptomatic therapy, of which antihistamines of the H_1 inhibitor type are the therapeutic mainstays. Hydroxyzine hydrochloride (Atarax, Vistaril), diphenhydramine hydrochloride (Benadryl), and cyproheptadine hydrochloride (Periactin) are the most effective. Of the three, hydroxyzine is the most potent, with recommended doses starting at 10 to 25 mg four times a day with upward titration. With excessive daytime sedation, 25 to 100 mg can be given at bedtime. Terfenadine (Seldane) with doses as high as 60 mg taken four times during the day can be used in combination with the more sedating H_1 antihistamines. Astemizole (Hismanal) just became available in the United States. It has an exceptionally long duration of action. This and another agent under investigation, ketotifen fumarate, might prove to be useful in refractory patients. Combination therapy should be attempted when single agents are insufficient. Cimetidine, an H_2 blocker, in combination with the H_1 antihistamines, can prove more effective than an H_1 antagonist alone in certain patients. Doxepin, an antidepressant with both H_1- and H_2-blocking properties, is potent in vitro and in vivo and can be given at doses of 25 to 75 mg at bedtime.

Sympathomimetic agents such as terbutaline sulfate, 2.5 to 5 mg three times a day, can supplement the antihistamines. In this respect it should be recalled that patients with acute, severe urticaria or angioedema often respond to subcutaneously administered epinephrine, 0.3 ml of 1:1,000 solution for adults. If the disease is severe and not responding to other forms of treatment, corticosteroids may prove useful. After an initial oral boost such as 45 to 60 mg daily for three to six days, tapering and alternate-day doses, such as 15 to 20 mg every other day, sustain the beneficial effect. Continuous steroid therapy is rarely necessary.

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Asthmogenic Drugs

ASTHMA IS A MULTIFACTORIAL DISEASE characterized by abnormal bronchial reactivity and may be perceived as wheezing, cough, chest tightness, or shortness of breath. Drugs may affect this hyperreactivity by any of several mechanisms. For example, drugs may alter bronchial reactivity through an immunoglobulin (Ig) E-mediated allergic mechanism or by the direct pharmacologic effect of a drug. We will focus on the second group of adverse reactions because they are repeatedly implicated in provoking occult or quiescent asthma and in increasing the severity of established asthma.

Foremost in this drug class are the β-adrenergic receptor blockers, which produce bronchoconstriction by directly blocking the β-receptor on the bronchial smooth muscle. This group currently has three main subclasses in clinical use: nonselective β-blockers such as propranolol or nadolol; β_1-selective (cardioselective) β-blockers—metoprolol, atenolol, for example; and β-blockers with intrinsic sympathomimetic activity, that is, partial agonists such as pindolol. All three classes have been shown to produce deleterious effects. Clearly, the first class produces bronchospasm at the lowest levels and should be avoided in patients with asthma wherever possible. The second was introduced partly because of this limit within the first class. The degree of effect on the β_1- versus β_2-receptors is relative, however, and a large enough dose of a selective drug will still produce significant β_2-blockade. The properties of the third group are less clear;